Strategies to enable same-day robotic urologic surgery

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Tackling challenges with innovation

AS SUMMER DRAWS TO A CLOSE, we head into the fall with the requisite return to school for students of all ages. There is always more to learn, and more ways to innovate, regardless of the field of study. As Urologists in Cancer Care™ Editor in Chief Raoul S. Concepcion, MD, FACS, writes in his editorial this issue, “the various facets of prostate cancer require the urologist in practice to stay abreast of the many advances and breakthroughs that are constantly being developed in order to stay current and provide state-of-the-art care.”

One innovation explored in this issue is that of same-day discharge (SDD) following robotic urologic surgery. In a highly informative article, Ronney Abaza, MD, FACS, outlines the strategies that have enabled him to greatly increase the rate of SDD for his patients.

“We have endeavored to progressively reduce hospitalization time after robotic surgery, and since 2016 have offered patients SDD after all types of robotic procedures, other than cystectomy, given the bowel used in diversions. In our first year of offering SDD, roughly 20% chose this option with gradual increases over time until now, when more than 95% of our robotic urologic surgery patients over the past 18 months were discharged within hours of their surgery, with no increase in readmissions or emergency department visits,” Abaza writes.

In bladder cancer, Benjamin J. Martin, MD, contributes an article about a 65-year-old man with upper tract urothelial carcinoma (UTUC). As with other areas in urology, the treatment of UTUC is noteworthy for the innovations seen in its treatment. “In just a few short years, the treatment options for upper tract urothelial carcinoma have changed considerably,” Martin writes.

In kidney cancer, Thai Ho, MD, PhD, writes about the importance of recognizing hereditary syndromes in renal cell carcinoma. “The early onset of cancers in hereditary syndromes emphasizes the need for regular surveillance to focus on primary preventive strategies to reduce morbidity and increase life expectancy in affected individuals,” Ho writes.

Finally, in this issue’s installment of our new Genomics Corner section, Concepcion interviews Urologists in Cancer Care™ editorial advisory board member and genetic counselor Rachelle Manookian, MS, CGC. In the interview, Manookian describes her career path, how the COVID-19 pandemic has affected her practice, and what alternatives are available to patients and providers when a certified genetic counselor is not readily available. Stay safe, and thanks for reading.

REFERENCE
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The challenges of prostate cancer management

HISTORICALLY, THE UROLOGY community has been the “gatekeeper” for the diagnosis and management of prostate disorders, malignant or benign. Prior to the advent of medical therapy and minimally invasive procedures to treat benign prostatic hyperplasia (BPH), if one were finishing their training and in search of a job opportunity, the litmus test to determine how busy a urologist was in practice was to ask how many transurethral resections of the prostate (TURPs) were being performed annually? If the number was more than 125 cases per year, that was considered a robust clinical practice. My recollection from my case log as a resident in the late 1980s was maybe 100 cases over a 4-year residency span, and I cannot fathom what that might look like today! The transition from open prostatectomy, TURP, medical therapy, and now minimally invasive procedures has required, to some degree, subspecialization to optimize outcomes rather than being the staple procedure for all urologists in practice.

The evolution in the diagnosis and management of prostate cancer has been equally complex. Akin to BPH, the various facets of the disease require the urologist in practice to stay abreast of the many advances and breakthroughs that are constantly being developed in order to stay current and provide state-of-the-art care. To that end—especially in larger independent practices, and certainly in academic centers—we have specialization in certain clinical areas within prostate cancer itself.

Diagnosis of prostate cancer
The early detection of prostate cancer remains critical and should always be in the hands of urology to educate the broader medical community. Mistakenly, we have applied the term screening to the various tests deployed. In its purest form, a screening test is used to aid in the detection of a certain disease in an asymptomatic population. A positive test suggests the high likelihood of that condition being present, and a negative test would indicate the absence of disease.1 Prostate-specific antigen (PSA) is not a good test for screening, but if it is used judiciously, it is still the linchpin in early detection of prostate cancer. Despite the controversial and subsequent reversal of the US Preventive Services Task Force (USPSTF) recommendations,2 most PSA testing is still carried out by primary care physicians in the United States.3 It is our role, as the subject matter experts, to educate our primary care colleagues on the limitations of PSA testing, as well as the following:

1. The goal of early detection is to identify those patients at risk for significant prostate cancer.
2. Current adjuvant testing to PSA, whether that be imaging or liquid-based testing.
3. Current advances in biopsy technique.

Localized prostate cancer
For decades, we have understood that if a man lives into his eighth or ninth decade of life, there is a strong likelihood that he will develop histologic prostate cancer, but not necessarily die of this disease. Most of these individuals will have a lower Gleason score and Grade Group disease, vis-à-vis, pattern 3 microscopically. Semantically, as we discuss prostate cancer with patients with newly diagnosed disease or colleagues, it is important for us to be more specific and base these
conversations relative to risk stratification. Because of the aforementioned USPSTF recommendation and the lay press, many of our patients—and referring primary care physicians—believe that prostate cancer does not need to be treated. We need to emphasize:

1. Active surveillance for low-risk disease is appropriate for initial therapy but does not mean that treatment will never be indicated.
2. The role of active treatment, either surgical or radiation, is still indicated in select risk groups.
3. Systemic therapies may also play a role in those with high-risk disease, especially in light of advanced molecular imaging.

Advanced prostate cancer
The major shift for many urologists over the past 10 years has undoubtedly been the understanding of how to treat advanced prostate cancer.

Advanced molecular imaging
The current and forthcoming approvals of various prostate-specific membrane antigen (PSMA) scans will markedly change the therapeutic landscape of the disease, especially as the approval may allow use in staging for high-risk/high-grade prostate cancer.

Theranostics
Close on the heels of PSMA approval is radioligand therapy, which is already approved overseas, and is soon to be approved in the US. Yet another agent in our armamentarium.

Genomic testing
Probably the hottest and least understood area, the incorporation of germline and somatic testing to manage and define risk will be standard of care. However, incorporating this into our practice models remains a challenge, but not an excuse to ignore at the present.

Supporting clinical trials
The number of unique agents and regimens (bispecific T-cell engagers, bipolar androgen therapy, androgen receptor transport disruptors/degraders, etc) continue to be investigated, with promising results early on. As our understanding of molecular drivers and resistance continues to increase through genomic testing, the promise of precision medicine may soon become reality.

REFERENCES
The FDA has converted the accelerated approval of frontline pembrolizumab (Keytruda) in advanced bladder cancer to a full approval and revised the indication to cover the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for any platinum-containing chemotherapy. In May 2017, the FDA initially approved pembrolizumab for the first-line treatment of patients with locally advanced or mUC who are ineligible for cisplatin-containing chemotherapy.

In 2018, the FDA updated the label for frontline pembrolizumab in this setting, with the approval now being specifically for the treatment of patients with locally advanced or mUC who are not eligible for cisplatin-containing chemotherapy. The label update was based on analyses from the phase 3 KEYNOTE-361 trial (NCT02853305), which was intended to be the confirmatory trial for the frontline accelerated approval of pembrolizumab in bladder cancer. The trial randomized patients with advanced or mUC to frontline treatment with single-agent pembrolizumab, pembrolizumab plus chemotherapy, or chemotherapy alone. Chemotherapy consisted of cisplatin or carboplatin plus gemcitabine. The coprimary end points for the trial were OS and PFS. Secondary end points were response, disease control rate, and safety.

The results showed that adding pembrolizumab to chemotherapy did not lead to a statistically significant improvement in overall survival (OS) or progression-free survival (PFS). Although there was a numerical improvement in OS and PFS with the combination versus standard chemotherapy, the difference did not achieve the threshold for statistical significance established in the trial design. Because the primary OS or PFS end points were not met with the combination, the study design did not allow for formal testing of the monotherapy arm.

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In the study, the median PFS was 8.3 months with P+C, compared with 3.9 months and 7.1 months with P alone and C alone, respectively. The HR for PFS for P+C versus C was 0.78 (P = .0033). The median OS was 17.0 months for P+C, compared with 15.6 months with P alone and 14.3 months with C alone. The HR for OS for P+C versus C was 0.86 (P = .0407). The objective response rates were 54.7%, 30.3%, and 44.9% for P+C, P, and C, respectively.

Regarding safety, 75.1% of the P+C arm experienced grade 3 to 5 treatment-related adverse events, compared with 16.9% in the P arm and 71.6% in the C arm. The AE-related discontinuation rates of any drug were 30.9%, 15.9%, and 18.1% in the 3 arms, respectively.

## References


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OVER THE PAST 2 DECADES, robotic surgery has grown in urology to become the most common method for surgical management of prostate cancer and more recently for partial nephrectomy. Robotic surgery is also increasingly being applied to renal cancers requiring radical nephrectomy as well, even for complex and locally advanced tumors such as those invading contiguous organs or extending into the vena cava. Despite increasing adoption of robotic surgery and many advancements in technology and techniques over the past 20 years, the perioperative care of the robotic urologic surgery patient has not evolved as rapidly.

Within the past few years, some groups have explored the feasibility of taking advantage of the minimally invasive nature of robotic surgery to reduce hospitalization time postoperatively. This includes exploration of same-day discharge (SDD) after robotic prostatectomy, which nationally continues to have a mean length of stay of greater than 1 day, and the potential for overnight stay or even same-day robotic partial nephrectomy, which is still typically associated with a 2- to 3-night stay after surgery.

We have endeavored to progressively reduce hospitalization time after robotic surgery and since 2016 have offered patients SDD after all types of robotic procedures other than cystectomy given the bowel used in diversions. In our first year of offering SDD, roughly 20% chose this option with gradual increases over time until now, when more than 95% of our robotic urologic surgery patients over the past 18 months were discharged within hours of their surgery with no increase in readmissions or emergency department visits (FIGURE 1). We have successfully instituted protocols for this at 3 different hospitals and most recently without residents, fellows, or advanced practice providers such that SDD is likely possible in most practice environments, although perhaps to differing degrees.

The delays in cancer surgery that resulted from the COVID-19 crisis during which nonemergent surgeries were prohibited in many states provide additional motivation to adopt SDD after robotic surgery given that this would allow continued surgical cancer care when the availability of hospital beds and inpatient staffing are strained. The following strategies are presented for enabling SDD, particularly by those more experienced surgeons who know their outcomes and have infrequent early complications that would require overnight stays.
**Benefits of SDD**
Because less than 1% of complications occur within the first 24 hours after robotic surgery, requiring overnight stays in all patients is more likely for reducing surgeon worry rather than benefiting patients. Most patients will prefer to recover in their homes, sleep in their own beds, eat home-cooked meals, and have their family around them rather than staying in a hospital as long as they know it is safe. Sleep has been shown to be important for recovery, but sleep disturbances experienced by patients on typical hospital wards have been shown to be worse than in an intensive care unit. Although challenging in the hospital often because of limited staffing, earlier ambulation is encouraged by SDD, which may reduce the risk of deep vein thrombosis and ileus. Lastly, in addition to saving hospital beds and staffing for other patients when hospital census is high, SDD reduces costs to hospitals given that they receive global payments for surgical encounters regardless of how long patients are hospitalized, and this may offset some of the additional costs of robotic surgery.

**Patient education**
Setting expectations is critical to patients being comfortable with SDD. We introduce the expectation of SDD as long
as everything goes as planned with surgery and anesthesia in the first patient encounter preoperatively and again in all printed educational materials, preoperative teaching by medical assistants, and by the surgeon in the preoperative area as well as with family postoperatively. Surgeons who have not attempted SDD before may be surprised by how often patients are pleasantly surprised that they will be allowed to go home on the same day as their surgery. Most patients either have experience with or know someone who has undergone outpatient surgery like laparoscopic cholecystectomy, hernia repair, or arthroscopy, and explaining that robotic surgery is very similar to these compared with traditional open surgery will help patients feel comfortable with SDD. Patients also need to know that if problems arise when they get home, they will have a safety net. Before surgery, we provide patients with a medical alert wallet card that has a phone number they can call 24 hours a day and instructs them to call before going to any ED with the opposite side having instructions (eg, catheter care) for other health care providers if they do end up in the ED or at an outside hospital.

Narcotic and drain avoidance

The benefits of narcotic avoidance include reduced ileus/constipation, confusion/sedation (especially in the elderly), nausea/vomiting, and risk of developing opioid addiction. We have successfully avoided intravenous narcotics in more than 5000 consecutive patients undergoing robotic surgery and allow oral narcotics but educate patients on the benefits of minimizing these. We routinely give ketorolac and place a belladonna and opium suppository before reversal of anesthesia and inject ropivacaine at all incision sites. Patients are discharged with 10 tablets of oral narcotic but instructed to use acetaminophen first and reserve narcotics for moderate to severe pain. Patients are told to medicate themselves with a goal pain score of 2 to 3 rather than 0 since it is normal to have some soreness after surgery, and injudicious amounts of narcotics would be needed to eliminate pain completely. More than half of our patients undergoing robotic surgery never end up using any narcotic tablets postoperatively. Additional options have been described for minimizing narcotics, and although we do not have experience with these, there may be benefits to using regional blocks (eg, transversus abdominis plane blocks), oral medications like gabapentin or celecoxib, intravenous lidocaine intraoperatively, or local injection of bupivacaine liposome injectable suspension.

Although some patients will not find home care of a drain to be a barrier to discharge, many patients will find this challenging particularly if also discharged with a bladder catheter (eg, prostatectomy). In addition, the presence of a drain will also reinforce the “sick role” in patients’ minds. Surgeons will also often default to overnight stay to allow drain removal prior to discharge because the vast majority of drains are used as a precaution and are removed the next day because no urine leak was present. Expert robotic surgeons should consider avoiding drains and evaluating their historical experience to determine whether they are necessary and can begin by selectively omitting drains when comfortable doing so and then transitioning to less and less...
use. We have performed more than 5000 robotic surgeries since adopting a routine of drain avoidance and used a drain in less than 1% of these patients even with known urinary tract violation, such as in prostatectomy, partial nephrectomy, nephroureterectomy, or ureteral reconstruction/plyoplasty. In our experience, we would need to leave more than 600 drains to avoid 1 urine leak and more than 2000 drains to avoid each instance that required a percutaneous drainage procedure postoperatively.

**Minimizing ports/incisions**
Many robotic and laparoscopic surgeons have minimized the effect of each incremental port on patient perception and pain, but the recent interest in single-incision robotic surgery since the introduction of the da Vinci SP (single port) robot has called into question the suggestion that additional ports do not affect postoperative pain and recovery. In our experience, single-incision prostatectomy was associated with a 15% reduction in pain scores compared with traditional multiport prostatectomy. In particular, ports placed through the rectus muscle likely increase pain disproportionately because of pain with any abdominal contractions such as coughing, bending over, and sitting up. Surgeons should endeavor to use as few ports as possible to safely accomplish their operation. Even before the SP robot, we routinely used only 3 ports for nephrectomy, pyeloplasty, adrenalectomy, and ureteral reconstructions for over a decade given that almost all can be accomplished without an assistant port. Given our experience with SP surgery, we have more recently transitioned to a routine 4-port robotic prostatectomy without requiring an assistant port and eliminating any ports through the rectus (FIGURE 2).

**Reduced pneumoperitoneum pressure**
The insufflation pressures typically used for laparoscopic and robotic surgery of 12 or 15 mm Hg are based on tradition and are not supported by evidence. We adopted a routine of using 6 mm Hg for robotic pelvic surgery in 2016 and have performed more than 1500 consecutive procedures at this level. We previously identified a reduction in pain with prostatectomy performed at 6 mm Hg compared with our historical series at 15 mm Hg. We recently conducted a randomized comparison of prostatectomy at 15 mm Hg vs 6 mm Hg and found less mean and peak pain scores, less shoulder and groin pain, and faster return of bowel function at the lower pressure (unpublished data). We recommend that surgeons use the lowest pressure at which they are comfortable operating, as most will not find any difference operating at 6 mm Hg. Of note, we perform kidney and other upper tract surgery more often at 8 mm Hg given that the bowel can be more intrusive when not retracted by gravity in Trendelenburg position. Whether lower pressure has enough effect on pain or ventilation parameters to improve the rate of SDD is unknown, but we recommend this for surgeons adopting SDD because the potential benefit outweighs any liabilities.

The minimally invasive nature of robotic urologic surgery allows the adoption of SDD protocols. Surgeons can consider these strategies to enable this and begin to offer SDD to their patients with a gradual increase in the rate of SDD over time.

**REFERENCES**


11. Ferroni MC, Abaza R. Feasibility of robot-assisted prostatectomy performed at ultralow pneumoperitoneum pressure of 6 mmHg and comparison of clinical outcomes vs standard pressure of 15 mmHg. *BJU Int. 2019;124(2):308-313. doi:10.1111/bju.14882*

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**CASE OF THE MONTH**

**BLADDER CANCER**

UTUC case illustrates rapidly changing treatment landscape

Urologists and medical oncologists should collaborate to customize therapy

by Benjamin J. Martin, MD

**THE CASE**

A 65-year-old man presented in early 2019 with gross painless hematuria. He has a history of T1 high-grade urothelial carcinoma of the bladder, status posttransurethral resection of bladder tumor (TURBT) times 2, each followed by an induction 6-week course of BCG and maintenance; he experienced good response with no recurrence documented for more than a year. Unfortunately, he has been lost to follow-up since his last negative office surveillance cystoscopy approximately 12 months prior to this episode.

**Medications:** amiodipine (Norvasc), lisinopril, atorvastatin (Lipitor), pantoprazole (Protonix)

**Allergies:** no known drug allergies

**Medical history:** hypertension, hypercholesterolemia, gastroesophageal reflux disease, psoriasis

**Social history:** former smoker (40 pack-years), quit after second TURBT

**Physical exam:** unremarkable, normal genitourinary exam and digital rectal exam

**Glomerular filtration rate (GFR):** 66 mL/min/1.73 m²

**CT urogram** showed 4-cm ill-defined hypoenhancement of the right lower pole, with subtle perinephric stranding. There was no lymphadenopathy.

**Cystoscopy:** no bladder recurrence

**Right ureteroscopy** confirmed papillary lesion occupying the entire lower pole calyces.

**Urine cytology:** positive for urothelial cancer

**WE ARE ALL** very familiar with the risk of local recurrence of high-grade urothelial cancer, but a recent meta-analysis of upper tract recurrence following radical cystectomy showed only a 0.75% to 6.4% risk. A strong argument could have been made for a cystectomy at this patient’s first high-grade T1 recurrence post BCG a few years ago. His recurrence was noted to be less than 3 cm in size and was unifocal, and no carcinoma in situ was present. If he had chosen the cystectomy route, he more than likely would have received standard-of-care neoadjuvant chemotherapy.

Would that have reduced his risk of upper tract disease? The role of neoadjuvant chemotherapy for upper tract urothelial carcinoma has not been established to the same degree as it has for bladder cancer. Current National Comprehensive Cancer Network guidelines do not recommend it as first-line therapy. A meta-analysis by Loew et al found support for both neoadjuvant and adjuvant chemotherapy in combination with radical nephroureterectomy, but the only randomized studies with level 1 evidence support adjuvant treatment.

Endoscopic management is generally reserved for smaller, low-grade lesions. Mitomycin administered via a unique gel (Jelmyto) is a new FDA-approved option that allows for a nephron-sparing approach in patients with low-grade tumors of the upper tract. A direct biopsy of the renal pelvis tumor was not done in this patient, but based on the history and the imaging characteristics, it was thought to be more likely than not high-grade, invasive disease. He also had no contraindications to definitive surgery that would necessitate nephron sparing. However, it is important to differentiate low- versus high-grade disease in light of this new approval.

The patient underwent a right robotic-assisted total nephroureterectomy in June 2019. His preoperative GFR was 66 mL/min/1.73 m², and immediately postoperatively, it had declined to 46 mL/min/1.73 m². The final pathology was read as a 5.3-cm high-grade urothelial cancer that invaded into the renal pelvis adipose tissue and renal parenchyma.

He was referred to medical oncology for adjuvant therapy. A fludeoxyglucose F 18–positron emission tomography (FDG PET) scan showed uptake in a few small pulmonary nodules and in portacaval lymph nodes, thought to be...
consistent with metastatic disease. With his reduced renal function, he was deemed not eligible for cisplatin-based therapy, which is included in the preferred regimens. Therefore, he was started on carboplatin and gemcitabine. Pancytopenia after 5 cycles necessitated a dose reduction; because of continued renal function decline, carboplatin was discontinued after the sixth cycle. A repeat PET scan at that time showed stable disease. The patient continued gemcitabine for 8 more cycles, but worsening renal function (GFR: 23) and thrombotic thrombocytopenic purpura caused cessation of therapy in August 2020. Repeat imaging confirmed progression of disease.

Pembrolizumab (Keytruda) is an FDA-approved monoclonal antibody immunotherapy directed against the PD-1 receptors on T cells. PD-L1 and PD-L2 ligands on tumor cells couple with T-cell PD-1 receptors to block T-cell function. By blockade of the PD-1 receptor, tumor-mediated immune suppression is prevented. Initial FDA approval required a PD-L1 expression combined positive score of 10% or more in the tumor tissue, but pembrolizumab may be used in patients regardless of PD-L1 expression if they are cisplatin ineligible, as is the case with this patient—although the objective response rate (ORR) is much less if the tumor has lower expression.

Enfortumab vedotin-ejfv (Padcev) is an antibody-drug conjugate against NECTIN4, which is increased on the cell surface of multiple subtypes of urothelial carcinoma. The phase 2 EV-201 trial (NCT03219333) included patients heavily pretreated with platinum-based agents and anti–PD-1/PD-L1 therapy, yet still showed an ORR of 44% and complete responses of 12%. Enfortumab vedotin is given intravenously on days 1, 8, and 15 of a 4-week cycle. Possible adverse events include fatigue, peripheral neuropathy, alopecia, rash, and decreased appetite. This patient opted for clinical trial and started therapy with enfortumab vedotin in September 2020. His renal function improved to 32 mL/min/1.73 m² on treatment. Imaging with FDG PET showed stable disease as of his last exam in May 2021.

In just a few short years, the treatment options for upper tract urothelial carcinoma have changed considerably. Urologists and medical oncologists should work together in a multidisciplinary fashion to tailor therapy to the specific needs of each patient. It should also be noted that upper tract urothelial tumors are a very common presentation for patients with Lynch syndrome. With that in mind, urologists need to be aware of genetic and somatic testing for Lynch syndrome and associated tumors, which include colorectal, upper gastrointestinal, endometrial, ovarian, and pancreatic cancers. Obviously, this can affect screening for these cancers and family counseling.

REFERENCES

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Recognizing hereditary syndromes in RCC

Patients may require specific diagnostic and therapeutic management

by Thai Ho, MD, PhD

HEREDITARY RENAL CELL carcinoma (RCC) may account for up to 8% of RCC, and extrarenal manifestations may present in early childhood. Establishing screening guidelines for hereditary RCC may help identify individuals at increased risk of developing extrarenal manifestations, which can vary. With renal and extrarenal manifestations, a referral to a multidisciplinary team ensures a long-term treatment plan is in place to monitor for complications. Furthermore, the early onset of cancers in hereditary syndromes emphasizes the need for regular surveillance to focus on primary preventive strategies to reduce morbidity and increase life expectancy in affected individuals.

Hereditary RCC syndromes have led to the discovery of key mechanisms underlying sporadic RCC and have become a foundation for the development of targeted therapy. As an example, von Hippel-Lindau (VHL) disease is an autosomal dominant disorder caused by germline mutations in the VHL gene. The most common sporadic RCC histology is clear cell RCC (ccRCC), which is also associated with VHL mutations. The VHL gene product, the protein VHL, acts as an oxygen sensor that regulates degradation of the hypoxia-inducible factors (HIFs). The HIF transcription factors bind hypoxia-related elements to activate target genes, such as VEGF, involved in how cells sense and adapt to low oxygen levels. As a result of these discoveries in VHL pathogenesis, the 2019 Nobel Prize (William Kaelin, MD; Sir Peter Ratcliffe, MD; and Gregg Semenza, MD, PhD) was awarded for elucidating how cells regulate blood vessel growth. These discoveries served as the foundation for antiangiogenic therapies (axitinib [Inlyta], bevacizumab [Avastin], cabozantinib [Cabometyx], lenvatinib [Lenvima], pazopanib [Votrient], sorafenib [Nexavar], sunitinib [Sutent], and tivozanib [Fotivda]) used in the treatment of metastatic RCC.

Given the autosomal dominant nature of inheritance in VHL disease, affected individuals have a 50% chance of having an affected child. Affected individuals may have a de novo germline VHL mutation or inherit a nonfunctional VHL allele from one of their parents. A subsequent secondary inactivation of the other allele is associated with the development of both renal (ccRCC) and extrarenal tumors (endolymphatic sac tumors, pancreatic neuroendocrine tumors, pheochromocytomas, and retinal/central nervous system hemangioblastomas). Even if a tumor is surgically removed, tumors can recur or new ones can develop over an affected individual’s lifetime because of germline mutations. Consistent with a hereditary RCC syndrome, the average age of ccRCC onset is 35 years in VHL disease, which is almost 30 years earlier than the age of onset in sporadic ccRCC.

Surveillance guidelines focus on physical examinations, blood tests, and imaging tests at specific time intervals to monitor existing tumors as well as evaluate for new tumors. Following established surveillance guidelines (www.vhl.org) can reduce the morbidity and mortality of persons affected by VHL disease.

The observed early onset of hereditary RCC indicates that primary preventive strategies are more likely to increase life expectancy in affected individuals than administering targeted therapies in the metastatic setting. The median age of individuals with sporadic RCC is 64 years in an analysis of the Surveillance, Epidemiology, and End Results (SEER)-17 registry program, which was considerably older than the median age of 37 years in an independent cohort of National Cancer Institute (NCI) Urologic Oncology Branch individuals affected...
by hereditary RCC. Individuals with hereditary RCC syndromes had median ages of onset ranging from 35 to 50 years. Because the median age of presentation for hereditary RCC is 27 years younger than for RCC observed in the general population, the NCI study suggested that individuals affected by RCC who are 46 or younger be referred for genetic counseling even in the absence of overt extrarenal clinical manifestations.

Patients with hereditary RCC syndromes require specific diagnostic, surveillance, and therapeutic management. Many of the clinical manifestations of hereditary RCC syndromes can be challenging for a clinician to recall. However, an early age of cancer diagnosis may be an initial clue to identify patients who may benefit from further genetic testing and referral to a multidisciplinary treatment team.

In the setting of a hereditary RCC syndrome, an adherence to established surveillance strategies, an appropriate management of the renal and extrarenal disease manifestations, and attention to at-risk family members will lead to improvement in clinical outcome. The observed early onset of hereditary RCC indicates that primary preventive strategies are more likely to increase life expectancy in affected individuals than administering targeted therapies in the metastatic setting. Individuals 46 years or younger affected by RCC should be considered for genetic counseling and germline mutational testing, even in the absence of secondary clinical manifestations. As life expectancy increases, additional clinical manifestations in hereditary RCC syndromes may become apparent, and management by a multidisciplinary team is warranted.

REFERENCES

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ADJUVANT PEMBROLIZUMAB DATA PUBLISHED IN NEJM AS FDA WEIGHS RCC APPROVAL

DATA FROM THE phase 3 KEYNOTE-564 trial supporting a potential FDA approval of adjuvant pembrolizumab (Keytruda) in renal cell carcinoma (RCC) have been published in the New England Journal of Medicine. The application for pembrolizumab the FDA is considering is specifically for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. The regulatory agency is scheduled to decide on the application on or before December 10, 2021.

The phase 3 KEYNOTE-564 (NCT03142334) trial showed that at a median follow-up of approximately 24 months, the median disease-free survival (DFS) was not reached with either adjuvant pembrolizumab (n = 496) or placebo (n = 498) as per investigator assessment; however, the HR for DFS showed that pembrolizumab induced a 32% reduction in the risk of disease recurrence or death compared with placebo (HR, 0.68; 2-sided P = .002). In the double-blind, multicenter, phase 3 KEYNOTE-564 study, investigators explored pembrolizumab vs placebo following nephrectomy in patients with clear cell RCC. Patients’ disease had to meet criteria that categorized them as high risk for recurrence, which included pT2, grade 4 or sarcomatoid, N0, M0; pT3, any grade, N0, M0; pT4, any grade, N0, M0; any pT, any grade, N-positive, M0; or M1 with no evidence of disease after surgery. All patients were randomized 1:1 to receive pembrolizumab at 200 mg every 3 weeks or placebo every 3 weeks, both for approximately 1 year. The primary end point of the trial was investigator-assessed DFS; secondary end points were overall survival and safety.

At 1 year, the estimated DFS rates were 85.7% and 76.2% with pembrolizumab and placebo, respectively. At 2 years, these rates were 77.3% and 68.1%, respectively. Regarding safety, all-grade adverse effects (AEs) with pembrolizumab occurred in 96.3% of patients and in 91.1% of those on placebo; grade 3 to 5 AEs occurred in 32.4% and 17.7%, respectively. AEs led to death in 2 patients on pembrolizumab and in 1 patient on placebo.

Treatment-related AEs (TRAEs) occurred in 79.1% and 53.4% of pembrolizumab- and placebo-treated patients, respectively. A total 18.9% of patients on pembrolizumab had a grade 3 to 5 TRAE vs 1.2% of those on placebo.

REFERENCE

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Genetic counselor discusses her role in patient care

Parents are seen for pre- and posttest counseling as well as second opinions

**THE AREA OF** genetics counseling is becoming increasingly important for patients and providers with the emergence of targeted treatments such as PARP inhibitors. In this interview, licensed genetic counselor Rachelle Manookian, MS, CGC, discusses her career path to genetic counseling and how her practice functions within her institution. She was interviewed by *Urologists in Cancer Care™* Editor in Chief Raoul S. Concepcion, MD, FACS.

**CONCEPCION:** Please tell us a little bit about your educational background and your journey to become a genetic counselor.

**MANOOKIAN:** I received my bachelor of science in biology from the University of California, Irvine (UCI) and a master of science in genetic counseling from the Icahn School of Medicine at Mount Sinai. I took a gap year between my bachelor’s and master’s programs, during which I worked as a teacher in an afterschool program for elementary, middle, and high school students. During that time, I also volunteered at a shelter for victims of domestic violence, completing client intakes and answering calls to the hotline. I had previously received my California-State Domestic Violence Advocacy training certificate and had worked with survivors of domestic violence for about 3 years.

In my final year at UCI, I had shadowed and worked with a local genetic counselor in the prenatal setting. These types of experiences relevant to genetic counseling skills (crisis counseling, advocacy work, teaching, shadowing) are valued in applying to genetic counseling programs. As it relates to education, many who pursue a genetic counseling degree have a bachelor’s degree in biology or psychology, but there are also other majors who enter the field having fulfilled the necessary prerequisites.

Genetic counseling master’s programs are generally 2-year programs, and graduates go straight into the workforce upon receiving their degree. There are currently 51 accredited genetic counseling programs in the United States and 4 accredited programs in Canada.

**RC:** What is your current position and areas of clinical interest?

**RM:** Currently, I work as a cancer genetic counselor at City of Hope Comprehensive Cancer Center (COH) in Duarte, California. Patients seen in our clinic range from affected patients with cancer [including those undergoing active treatment as well as patients who are NED (no evidence of disease)] to unaffected individuals with a strong family history of cancer. I have a special interest in prostate and other genitourinary cancers; however, the genetic counselors at COH see the full spectrum of cancer types/indications.

**RC:** How does your practice function in the overall structure at COH?

**RM:** Our Genetics Division comprises a multidisciplinary team of genetic counselors, physicians, and nurse practitioners with support of genetic counseling assistants and a clinic coordinator. We see patients for pretest counseling, posttest counseling, second opinion visits (patients who have had testing at another institution), and our physicians have long-term follow up with high-risk patients.

Our referrals are by and large internal for patients who are either actively treated at COH or were previously treated here and are now being surveilled. We do have external referrals from community providers, primary care physicians, etc, as well as patients who
self-refer for genetic testing. We have urgent slots for patients who need genetic testing for treatment decisions (e.g., surgery, targeted therapy). Our genetic counselors also have built strong relationships with providers from various specialties within COH by attending tumor boards and through other involvements on campus; providers can reach out to us if any special accommodation is needed for their patient(s).

**RC:** How has the COVID-19 pandemic affected your practice and the role of telehealth?

**RM:** Our clinic fully converted to telehealth (phone or video) in March of last year at the beginning of the pandemic. Fortunately, the genetic testing laboratories we work with were able to mail saliva kits for genetic testing directly to patients’ homes to reduce any potential COVID-19 exposure risk. We have now added a number of in-person appointments per month for patients who either cannot have a visit by telehealth or may need a physical exam as a part of their genetics work-up.

**RC:** Given the paucity of certified genetic counselors (GCs) in the US but the increasing demand as clinicians adopt testing protocols, what are some alternative solutions that are available to patients and providers, especially if a certified GC is not readily accessible?

**RM:** This is absolutely an important consideration. Some genetics clinics have 12–plus-month wait times, unfortunately. As such, alternative solutions are necessary. Alternative service delivery is an active area of research to figure out creative ways for patients to be appropriately informed in a scalable way. There are clinicians (oncologists, nurse practitioners, etc) who have completed training such as the City of Hope Intensive Course who can provide hereditary cancer risk assessment, order appropriate testing, and give results and recommendations. There are other programs/certifications that provide a similar type of training. I highly encourage providers to identify champions in their clinics who would be interested in pursuing this and providing this care to their patients.

Additionally, some providers at institutions who have genetic counselors can actually order the genetic testing and then refer to their genetic counselors after the fact. By building this relationship with genetic counselors within their institution, I believe nongenetics providers can find a way to offer genetic testing to their patients in a setting that allows the patient to be informed while also receiving the care that they need in a timely manner. The nongenetics providers should also be prepared to identify patients who may need a referral for more counseling before the testing is ordered (e.g., patients concerned about genetic discrimination, cost of testing, etc). If genetic counselors are not available within the institution but are local, clinicians should work collaboratively with these local genetic counselors to figure out a process that works well for all involved.

Lastly, some genetic testing laboratories are able to offer genetic counseling as a part of their services, so providers can also reach out to genetic testing labs to learn more about their offerings and the best way to implement testing in their clinics with appropriate resources for patients both before and after testing.

**“How does your practice function in the overall structure at COH?”**

**RAOUL S. CONCEPCION, MD, FACS**

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**RACHELLE MANOOKIAN, MS, CGC**

**RC:** What would you list as the most important/critical take-home message(s) for our readers as it relates to genetic counseling and testing?

**RM:** I would encourage all providers in the oncologic setting to familiarize themselves with indicators for genetic testing in their patients. For example, the National Comprehensive Cancer Network recommends germline genetic testing for patients whose prostate cancer is metastatic, intraductal, high-, or very high-risk group. If you have one of these patients, they are a candidate for germline genetic testing. If they have a germline mutation, this may affect not only them but their entire family as well. Family members being informed about increased cancer risk due to a genetic mutation can lead to early detection, and, in some cases, prevention of cancer. Next, providers should be prepared with options for these patients to get the genetic testing they need. If referral to a genetics provider is not possible because of geography, wait times, or other concerns, clinics should aim to have an internal clinician who is informed about hereditary cancer genetic testing and can appropriately order testing and interpret results.
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